

THE PRESENT STATUS OF ULCERATIVE COLITIS AND REGIONAL ENTERITIS*

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WITH the accumulation of experience and the improvement of diagnostic criteria, it has become more and more evident that there are many forms of ulcerative enteritis. All forms of ulcerative enteritis assume in their very nature the status of chronic disease. Hence, the terms "chronic ulcerative colitis" and "regional enteritis" are best used to denote general clinicopathologic syndromes, rather than to designate one of the several specific disease entities in which these syndromes are present.

In medical practice it becomes necessary to study chronic ulcerative colitis and enteritis according to etiologic types, and the first and most fundamental clinical effort should be directed at determining the specific etiologic factor responsible for the development of the syndrome in a given case. The infection may be caused by one or more of several bacteria or animal parasites, in association with certain dietary and constitutional deficiencies, or by other and some still unknown conditions.

We now recognize a variety of inflammatory intestinal conditions. Some of them are strictly localized to the large intestine, others to the small and still others may involve both small and large intestine. It is well, always, to keep this in mind when studying a given case. The concept, advanced by a few, that ulcerative colitis and regional enteritis are all "of a piece" is, in the light of present knowledge, no longer tenable. One must rather think in terms of many disease entities, each having this or that cause with these or those pathologic features and in turn clinical manifestations. If these facts are kept in mind a more rational treatment may be instituted.

TYPES OF COLITIS AND ENTERITIS

Strictly speaking, all forms of colitis, ileitis and jejunitis are forms

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of enteritis. However, by common usage the tendency of referring the term enteritis to the inflammations of the small intestine has developed. It is well understood, however, that some forms of ulcerative colitis, although primarily inflammations of the large intestine, may advance orad to involve the distal segments of the small intestine. So also may some primary inflammations of the small intestine advance caudad to involve the large intestine. For practical purposes, however, it is best to discuss separately (1) the lesions primarily confined to the large intestine, (2) those primarily confined to the small intestine and (3) those regional inflammatory conditions which have, in their very nature, a tendency to spread to involve both small and large intestine.

Streptococcal ulcerative colitis: The most common condition of the group involving primarily the large intestine is that commonly referred to as "nonspecific" or "idiopathic" ulcerative colitis. If physicians using the term would apply it to a single disease entity, well and good, but unfortunately a variety of ulcerative intestinal conditions are included under this designation. In fact, some writers include under it all cases of ulcerative colitis which are not of amebic or tuberculous origin. Consequently, the term becomes no longer tenable. The terms "colitis gravis" and "thrombo-ulcerative colitis" are descriptive of the serious nature of the disease and its pathologic inception, and go far in depicting a disease entity. However, since in this discussion I shall aim to give definite status to each form of ulcerative enteritis, I shall refer to this type as streptococcal ulcerative colitis.

This disease has characteristic pathologic manifestations, and hence typical proctoscopic and roentgenologic features. Its lesions begin in the most distal segment of the rectum, just above the anal canal. Diffuseness of involvement of the bowel is its pathognomonic feature. Whether 1 inch (2.5 cm.) of the lower part of the rectum or 5 feet (1.5 meters) of bowel are involved, the involved segment always is affected in its entirety, its entire circumference and the deeper layers of the wall and the mucosa secondarily. This gives the granular, easily bleeding mucous membrane so characteristic of this lesion. The disease tends to spread upward until the entire colon, and even the lower part of the ileum in the late stages of the disease, become involved. Since it is primarily a disease of the intestinal wall, a very characteristic roentgenologic picture develops. The bowel becomes diffusely narrowed, haustral markings are erased, the flexures and curves become more

angulated and the result is a smooth tube. In this, streptococcal ulcerative colitis differs from all other forms of ulcerative intestinal disease, except perhaps regional enteritis when it is confined to the distal portion of the ileum. The latter condition has, however, many features to distinguish it from streptococcal ulcerative colitis. Because of the relatively high incidence of the streptococcal form of ulcerative colitis, and because of the consistency with which its clinical, proctoscopic and roentgenologic manifestations conform to a certain pattern, I am inclined to use this type of ulcerative colitis as a norm and to describe other types chiefly by noting in what respects they differ from it.

This form of ulcerative colitis manifests itself in a variety of ways but in general the clinical manifestations follow one of three general courses. When the lesions are limited to the lower segments of the large intestine, particularly the rectum and rectosigmoid, the onset of symptoms can be described as insidious. The patient may have normal motions of the bowel but in addition may pass two or three or many bloody, purulent rectal discharges. He may not have any other important systemic symptoms except that he will gradually begin to speak of not feeling well. His complaint of not feeling up to par may increase gradually as the number of rectal discharges increases and ultimately a mild form of diarrhea may develop.

The second common onset may be classified by saying that the symptoms are severe. The patient may start rather suddenly with bloody diarrhea, low gradual fever, gradual loss of appetite and with them loss of weight and all the concomitants of a moderately severe illness. All the symptoms may start in a fulminating manner with an onset almost like that of lobar pneumonia or other similar serious illness. There will be a high fever, massive discharges of bloody material from the rectum, great prostration and rapid depletion.

A patient's symptoms may remain in the insidious form for months and years and then at the time of an infection of the upper part of the respiratory tract, some other intercurrent illness or perhaps some severe nervous trauma, there may be a sudden exacerbation of the disease and a change to a severe or even the fulminating form. The question is often raised whether these are different diseases or stages of the same disease. Experience seems to indicate that these are stages of the same disease attacking patients in various ways. Thus, one must be ever on the alert for the occurrence of this disease in these several forms so

that it may be distinguished carefully from the types of colitis which are to be discussed presently.

Amebic ulcerative colitis: Another type of colitis in which the lesions are limited to the large intestine is that caused by *Endamoeba histolytica*. Here the lesions are localized primarily to the cecum and possibly the flexures of the large intestine, although the entire large intestine may be involved. If the disease has advanced sufficiently toward the rectum so that lesions are visible in its mucous membrane, they present a very characteristic appearance. The ulcers give the impression of being punched out, with raised edges covered by a fleck of mucus and a hyperemic zone around the individual ulcer. Between the ulcers the mucous membrane is relatively normal. The disease largely affects the mucosa instead of the wall and there should be little difficulty in distinguishing this type of ulcerative colitis from the streptococcal variety of ulcerative colitis. Its extension is exactly opposite to that of the latter. Its lesions start in the cecum and spread caudad instead of starting in the rectum and spreading orad as do those of the streptococcal variety of colitis. Consequently, the symptoms are quite at variance to those of the streptococcal variety. Bleeding occurs relatively late in the disease instead of being present as one of the first symptoms. The severe prostration of the fulminating type of ulcerative colitis is observed rarely. The patient is usually in a relatively good condition. Roentgenologic examinations, too, show a rather characteristic deformity of the large intestine when the disease is sufficiently advanced. However, even early in the disease there may be the characteristic features in the cecum: namely, some narrowing and irritability when no other colonic lesions exist. With the progress of the disease the cecum becomes coned or narrowed to a point and the entire ascending colon may be narrowed irregularly. This is not a smooth diffuse narrowing such as one sees in the streptococcal type of ulcerative colitis. As the rectum is approached, there will be less and less roentgenologic evidence of disease except in those cases in which the greatest disease is at the flexures or in unusual segments.

Ulcerative colitis due to the virus of venereal lymphogranuloma: A third form of ulcerative colitis in which the lesions are limited to the large intestine is that caused by the virus of venereal lymphogranuloma. Here again the lesions start in the rectum and distal segments of the large intestine. The disease is also of the wall of the bowel but involves

not only the wall but the lymphatic structures around it and so there develops a condition in which a stiff tube having the feel and giving obviously the appearance through the proctoscope of perirectal inflammation exists. There may be multiple small sinuses from the mucous membrane to the deeper structures and so a rather definite proctoscopic and roentgenologic picture results. The disease will be limited to the rectum and rectosigmoid structures and the normal bowel will be reached much more abruptly than in the streptococcal variety. Almost invariably the patient will feel generally well and his complaints will be largely in reference to the local rectal condition. The diagnosis in this type of case will depend largely on the history of previous venereal infection, possibly the presence of buboes and among women very commonly the presence of preceding vulval lesions. The Frei reaction will be positive. But even if these conditions exist, the diagnosis of colitis due to the virus of venereal lymphogranuloma is not tenable if characteristic lesions of the rectum do not exist.

Regional ulcerative colitis: The fourth type of ulcerative colitis in which the lesions are limited to the large intestine is one of which the cause is not clear. We speak of it as a regional type of ulcerative colitis. The lesions involve isolated segments of intestine and may involve any segment, much in the manner of regional ileitis except that here the site of the disease is the colon. The lesion may be subacute or chronic and usually is quite destructive but also there may be evidence of hyperplastic changes. Commonly segments of the intestine from 6 to 12 inches (15 to 30 cm.) long are found to be involved with perfectly normal bowel distal and proximal to the lesion and always the rectum is not involved. In other words, this segmental type of colitis involves regions of the large intestine above the view of the sigmoidoscope. The wall of the involved segment is *also* stiff and thickened but the involvement is not as diffuse, regular and smooth as in the streptococcal type of ulcerative colitis. Thus, the roentgenologic examination is the most important objective method of establishing a diagnosis. Usually such a regional type of colitis remains localized to a segment of large intestine for months and years. Very occasionally, however, it has been known to spread orad and caudad so that ultimately even the distal portion of the ileum has become involved. The latter has initiated a difficult situation, indeed, and has always brought up the question whether this and so-called regional ileitis may not be the same or closely related condi-

tions. However, the fact that the condition usually remains localized to the large intestine, whereas regional ileitis commonly spreads from the ileum proximad to involve the jejunum and distad to involve the cecum and ascending colon, raises a very definite question of their being separate entities.

Regional ileitis: The two conditions commonly starting and having a tendency toward being confined to the small intestine are regional ileitis and intestinal tuberculosis. Both of them, if they are separate entities, are inclined to remain localized to the small intestine. In both of them, the infection is inclined to spread orad and caudad, thus ultimately involving parts of the large intestine and particularly the ileocecal coil. Thus, for the first condition the term "regional ileitis" becomes particularly suitable. When one speaks of this, one is referring to a subacute or chronic, destructive, exudative and proliferative regional inflammatory process commonly and perhaps usually beginning in the distal portion of the ileum. The name now refers to a definite disease entity well described by Crohn, Ginzburg and Oppenheimer¹ in 1932. In many respects the onset and clinical course of this condition are similar to those observed in the cases of regional colitis. However, patients suffering from the latter condition are prone to be much sicker than those who have regional ileitis. The onset of the disease is usually insidious but by the time medical aid is sought, well pronounced features of advanced disease are frequently apparent and the diagnosis can be readily established.

As with so many chronic infections of a proliferative and destructive nature, the story frequently begins with the complaint of fatigue, general malaise and loss of weight. Associated with these symptoms, or soon after their onset, a patient will complain of a mild, usually intermittent, type of diarrhea. The stools will be loose and watery, and defecation will be associated with cramps. Periods in which normal or even hard, dry stools are passed may alternate with diarrhea. The story in these respects is similar to that of a patient who has intestinal tuberculosis. As a rule, however, in cases of regional ileitis, progression to the next phase is more rapid and symptoms are more severe than in cases of intestinal tuberculosis. In the former, attacks of abdominal pain supervene and the pain may be of the dyspeptic or obstructive type from the first. In either event, obstructive features will soon predominate.

Generally speaking, there are four phases of the disease. The earliest

manifestation is that of an acute inflammatory process. As the terminal portion of ileum is the most frequent initial site of the disease, irritation of this portion of the intestine and its adjacent peritoneal covering produces a picture difficult to distinguish from acute appendicitis. The most common symptoms are fever of low grade, leukocytosis, nausea, vomiting, and tenderness and pain in the epigastrium or right lower abdominal quadrant. Diarrhea and cramps are unusual at this stage of the process.

As the disease advances, intermittent attacks of diarrhea are characteristic. The typical syndrome of enteritis of low grade then prevails, for the patient has fever, anemia and a palpable mass in the right lower abdominal quadrant and has lost weight; his stools are loose or watery and if any pain is present it is mild and colicky.

Remission of symptoms is common in the two stages described, but as the stenosing effects of the disease increase, the periods of relief are shorter and occur less frequently. The symptoms typical of intestinal obstruction are superimposed on those of chronic enteritis. The attacks of diarrhea are more profound and are accompanied by severe abdominal cramps, borborygmus, abdominal distention or visible contracture of the coils of the small intestine proximal to the diseased segment. Malnutrition and anemia become prominent features since much of the nourishment and fluids is lost because of the diarrhea. Furthermore, intake may be greatly limited on account of persistent nausea or even vomiting.

The fourth and final phase of the disease is attained when either acute obstruction is superimposed on the chronic condition or perforation of the bowel occurs and there ensues the formation of an abscess or fistula. The fistula may communicate with an adjacent portion of the intestine, with other viscera or with the abdominal parietes. The debility occasioned by the sepsis and deprivation of nutritional elements and fluids assumes great significance and in itself may be the terminating factor.

The course of regional enteritis as delineated is uniform only in a very general way. In the individual case the first signal of impending trouble may be the onset of the syndrome of the late phases, or the symptoms may have progressed from an occasional episode of pain in the right lower abdominal quadrant or the epigastrium to intestinal occlusion, although there may have been little intervening disturbance.

In an occasional case the chief complaint will be the one which is only remotely associated with the malady.

These facts and others to be mentioned concerning the pathologic changes of the diseased segment of bowel give further evidence of the destructive, proliferative and progressive nature of the disease. Generally speaking, when one first sees these patients the disease is in the advanced stage and the pathologic process already has produced unmistakable gross deformity. There is evidence of attempted fibrotic repair associated with chronic inflammation on which acute exacerbations of the disease have been superimposed. Pathologic descriptions of the condition have been comparatively uniform. The terminal portion of ileum, as has been indicated repeatedly, is the segment most frequently involved. Thickening of the wall of the bowel, narrowing of the lumen of the bowel and ulceration of the mucosa with the formation of pseudopolyps are noted. These associated characteristics have been described often as granulomatous ileitis. The character of the lesions may range from subacute to chronic. At times the intestinal wall is greatly thickened by edematous infiltration. Pseudotubercles, in association with large foreign body giant cells, are common. Perforation with the formation of an abscess is fairly common. As a result of this, multiple communicating fistulas may develop. These are the result of chronic perforation which takes place so slowly that time is allowed for segregation of the process from the peritoneal cavity and usually small walled-off abscesses form. These, in turn, discharge their content into a neighboring viscus. Grossly, the most striking features are typical enlargement and loss of flexibility of the affected segment of bowel and shortening and great thickening of the mesentery, in which the regional lymph nodes are large and firm. The tissues have a dusky, bluish red appearance and a phlegmonous exudate is distributed over the serosal surface of the intestine.

In the instances in which the condition is of long standing, many exacerbations usually have occurred and a large phlegmonous mass may have resulted. It is often very difficult to separate such a mass from the surrounding structures. At times, too, such lesions may affect the bowel in segmental fashion with relatively normal uninvolved segments lying between the involved portions. The involved segments are readily distinguishable from the normal portions by their loss of elasticity and soggy hoselike appearance. The microscopic appearance of the lesion

does not have any characteristics which distinguish it from other chronic inflammatory processes. Cells of the lymphoid series appear to predominate, except in the earlier, more acute stages. In the chronic process, the small lymphocyte, plasma cell and fibroblastic elements are in the ascendancy; eosinophils may be present. Submucous lymphoid follicles are usually very numerous. Giant cells are encountered frequently and often contain crystalline or lipoid particles. Focal collections of lymphocytes under the serosa with the giant cells here and there make the picture simulate tuberculosis.

Tuberculous ileocolitis: Another type of enteritis attacking primarily the small intestine is that due to *Mycobacterium tuberculosis*. The disease may be of the nature of extensive enteritis involving stretches of the intestine with rather normal segments of bowel between. The ulcers will be distributed irregularly and associated with lesions visible on the serous surface of the bowel and with miliary tubercles. The most extensive lesions will usually be in the distal segment of the small intestine and may extend to involve the cecum and other segments of the large intestine. This infection commonly attacks the ileocecal coil and it is at this point that the disease has its greatest activity. Only in the late stages will the lesions progress sufficiently caudad to be visible through the sigmoidoscope. Thus, the roentgenologic features will show characteristic irritability with rapid emptying and filling of the ileocecal region and great irregularity of the intestinal lesions will be observed in the roentgenogram. The smooth contour of the intestinal wall so commonly seen in the streptococcal type of colitis is not present in tuberculous ileocolitis. The disease again involves the mucosa more than the wall.

Other intestinal conditions: Other intestinal conditions which may or may not be of the nature of inflammatory disease are the following: (1) chronic bacillary dysentery; (2) ulcerative colitis of unknown cause (for those who still cling to the term nonspecific or idiopathic, the term might be applied to this group of cases); (3) a deficiency syndrome; (4) so-called allergic colitis.

There is a form of ulcerative ileocolitis which follows in the wake of severe bacillary dysentery due to one or several of the strains of *Shigella paradysenteriae*. Penner and Bernheim² have shown recently that the lesions of bacillary dysentery are in the nature of toxic reactions mediated through a sympathotonic reaction. This might explain

the fact that the lesions are also irregular and disseminated. In the occasional case in which extensive destructive ulcerative disease occurs, secondary invaders may be responsible for the late lesions. When lesions are visible through the sigmoidoscope, their irregularity as far as size, extent and mucosal appearance are concerned is particularly striking. It has been said that they are characteristic because of their irregular and yet extensive distribution. The same impression is gained from the roentgenologic appearance of the bowel in these cases. Still, the diagnosis will depend largely on the presence in the blood of agglutinins (in significant titer) of one or several strains of *Shigella paradysenteriae*.

One is particularly impressed with the latter fact when encountering cases of ulcerative ileocolitis belonging to the group which I have designated as of unknown cause. Here again the ulcerative disease may be extensive, involving long stretches of small and large intestine, or it may involve only the rectum and sigmoid. Whatever segment is involved, the appearance of the lesions is at variance with those of the conditions described having a specific cause and strikingly at variance with the appearance of the bowel in the streptococcal variety of ulcerative colitis. Agglutination of *Shigella paradysenteriae* will be absent. Culture made from the lesions and examinations of the stools will not be diagnostic. The lesions will be distributed irregularly and tend to resemble those of amebiasis or tuberculosis. Yet, usually one will detect differences. The differences are sometimes hard to describe, and it has been said that the ulcers are characteristic by being so uncharacteristic. The same thing will hold true as far as the roentgenologic examination is concerned. This is the group of cases that will particularly tax the physician's ingenuity and the response to one form of therapy or another will often be minimal. In these cases, too then, surgical intervention will more often be employed.

The type of intestinal disorder of the nature of a deficiency syndrome, other than sprue and pellagra, should actually not be discussed here. It is brought up only because there are still some who feel that the deficiency state plays a primary role in some of the types of ulcerative colitis which have been discussed. The history of patients suffering from an intestinal disorder in which a food deficiency is important is usually characteristic. Such persons may have gone for months and years on an inadequate dietary regimen. The result may be atrophy of

the intestinal wall. The appearance of the bowel through the sigmoidoscope may suggest diffuse hyperemia. No real ulcers will be present. The roentgenogram may show dilatation of the large intestine with minimal changes of the mucosal pattern in the form of what appears to be a "fuzziness" of the mucous membrane and in the small intestine a typical pattern of barium puddling and segmentation will be observed.

What has been said about the deficiency syndrome affecting the intestine might also be applied to so-called allergic colitis. Everyone will accept the fact that there are patients who exhibit symptoms of intestinal allergy. Few will be impressed by the thought that such allergy is a primary factor in ulcerative intestinal disease. It seems obvious that occasionally in severe cases of intestinal allergy, mucosal abrasions may occur so that ulcers of a transient nature may be present. There is, however, little or no evidence available that these form the basis of a type of ulcerative colitis. It would seem better to consider intestinal allergy as a condition quite apart from the big problem of ulcerative enterocolitis, in the realization that it may play a part in many ulcerative intestinal inflammations but that it is not necessarily causative in any of them.

CONCLUSIONS

This discussion emphasizes the fact that there are many varieties of ulcerative enterocolitis. One cannot emphasize too strongly the importance of establishing as nearly as possible the nature and cause of a given case. Each type recognized to date has some characteristic features which set it apart from the others. In the streptococcal variety, the diffuseness of involvement and the typical proctoscopic and roentgenologic pictures together with the finding of the streptococcus are important. In the amebic, the finding of *Endamoeba histolytica* is of the greatest importance. In tuberculous colitis, the presence of *Mycobacterium tuberculosis*, together with the history and finding of tuberculosis elsewhere, is of great value. In the cases due to *Shigella paradysenteriae* significant agglutinin titer of the blood serum is significant. In the cases due to the virus of venereal lymphogranuloma, the positive Frei reaction and the characteristic appearance of the lesions are essential. In the regional types and the groups still of unknown cause, continued and careful study is essential. It is important that these be not

confused with those forms of ulcerative colitis of specific cause and characteristic features.

R E F E R E N C E S

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